

Stimulating Peripheral Activity to Relieve Conditions (S.P.A.R.C.) Common Fund Program

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NIH



National Institutes
of Health

Electroceuticals/Bioelectronic Medicines: A Novel Therapy?

NATURE | COMMENT



Drug discovery: A jump-start for electroceuticals

Kristoffer Famm, Brian Litt, Kevin J. Tracey, Edward S. Boyden & Moncef Slaoui

Affiliations | Correspondence | [Full text](#)

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The New York Times

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MAGAZINE

15 COMMENTS

Can the Nervous System Be Hacked?

By MICHAEL BEHAR MAY 23, 2014

a research roadmap

Karen Birmingham, Viviana Gradinaru, Polina Anikeeva, Warren M. Grill, Victor Pikov, Bryan McLaughlin, Pankaj Pasricha, Douglas Weber, Kip Ludwig and Kristoffer Famm

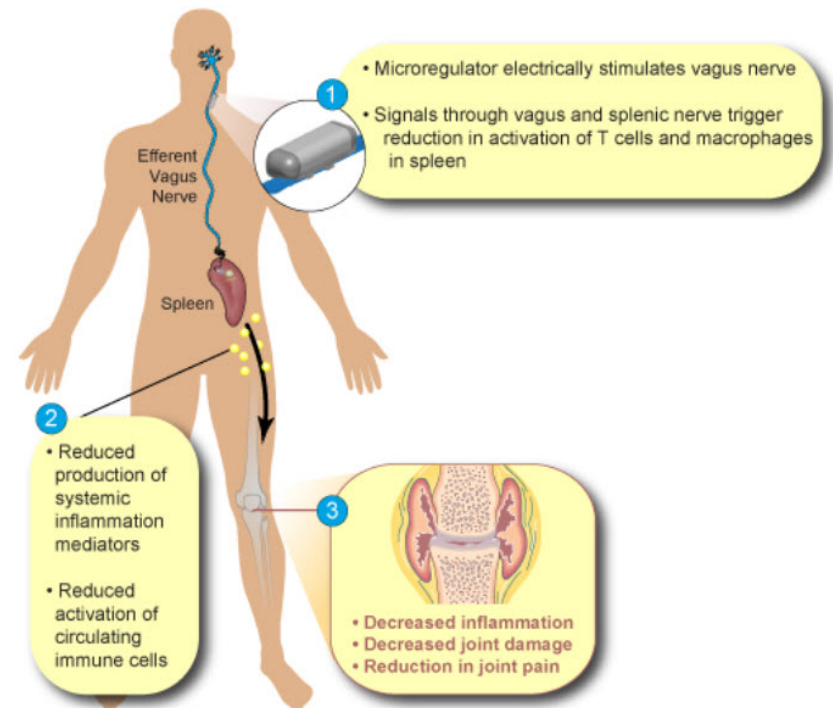
Realizing the vision of a new class of medicines based on modulating the electrical signalling patterns of the peripheral nervous system needs a firm research foundation.

Borovikova/Tracey 2000

letters to nature

Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin

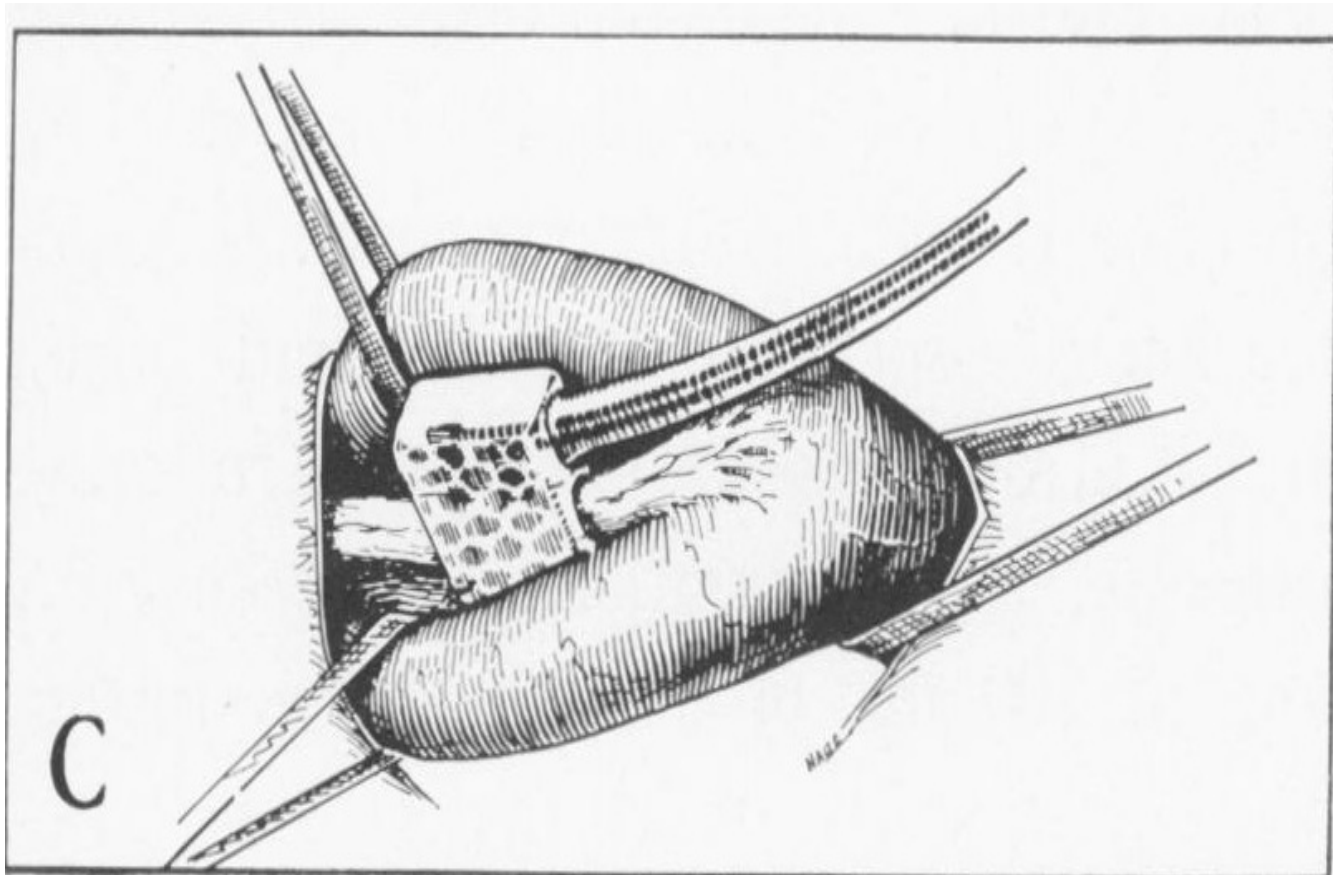
Lyudmila V. Borovikova*, Svetlana Ivanova*, Minghuang Zhang*, Huan Yang*, Galina I. Botchkina*, Linda R. Watkins†, Haichao Wang‡, Naji Abumrad§, John W. Eaton¶ & Kevin J. Tracey§



Source: <http://www.setpointmedical.com/index.php/technology>

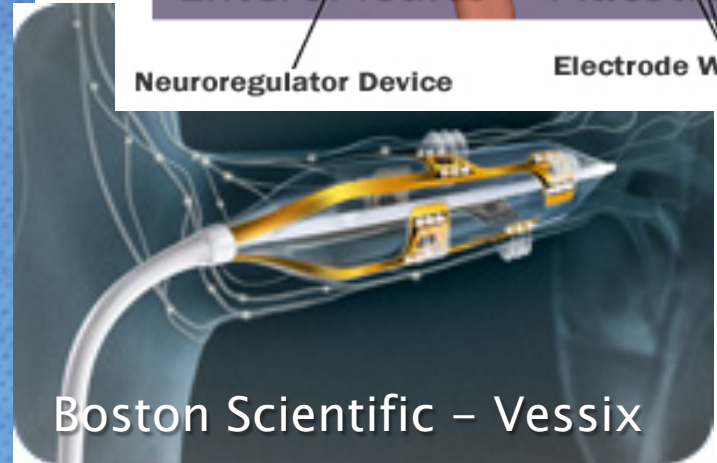
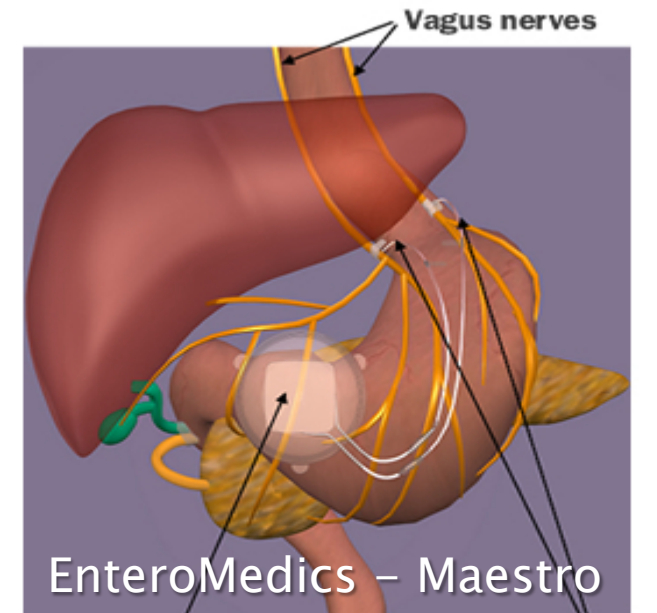
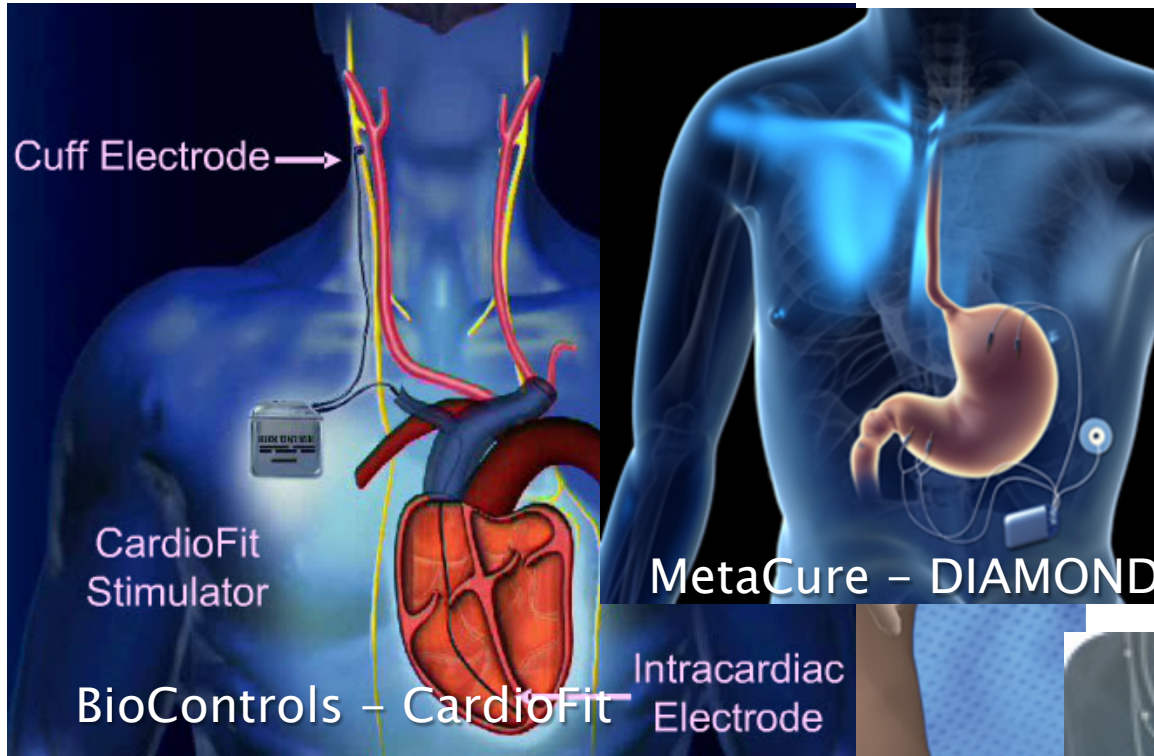
Carotid Sinus Nerve Stimulation

Braunwald 1970

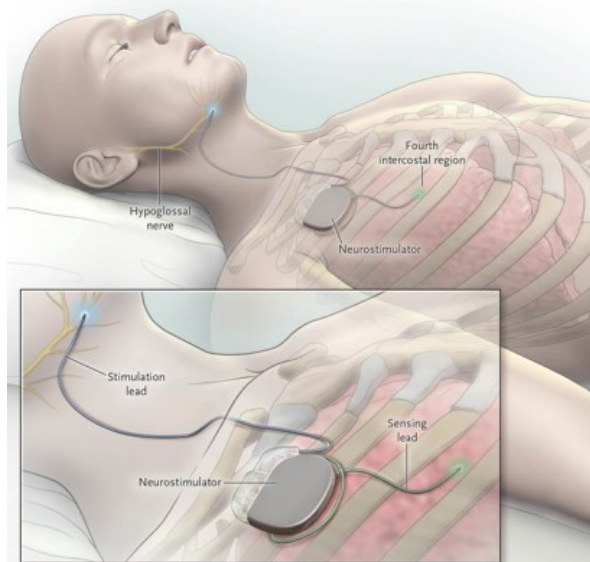


Original work in cats done by
Schweitzer 1948!

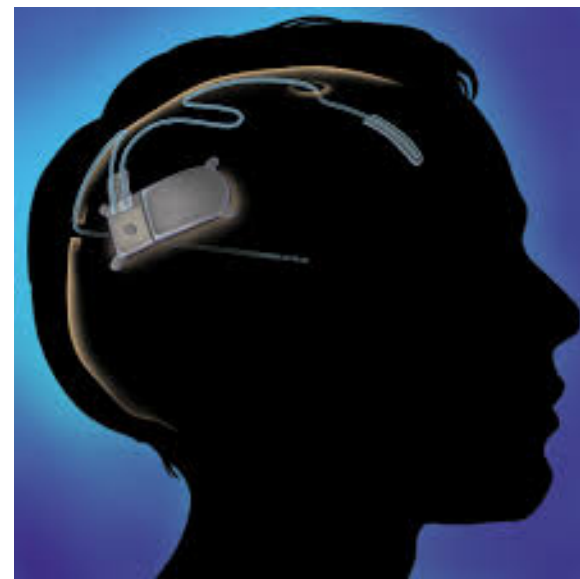
Bioelectronic Medicines or Neuromodulation?



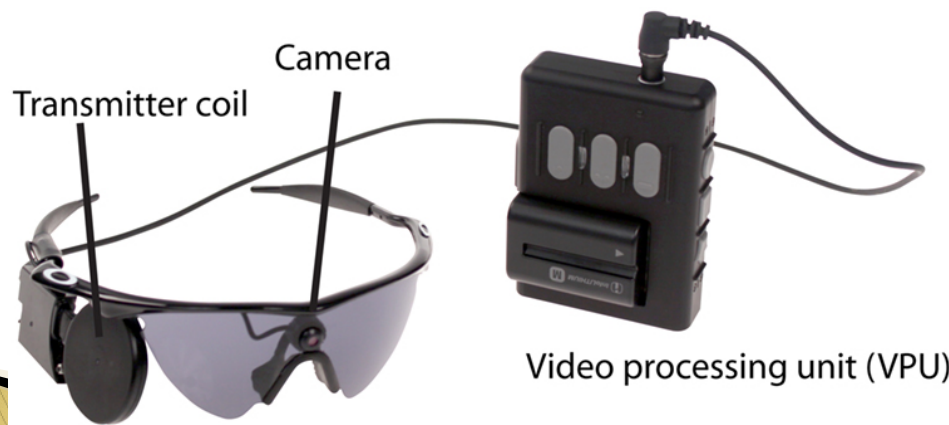
Recent U.S. Neuromodulation Approvals: RCT Pivotal Trials



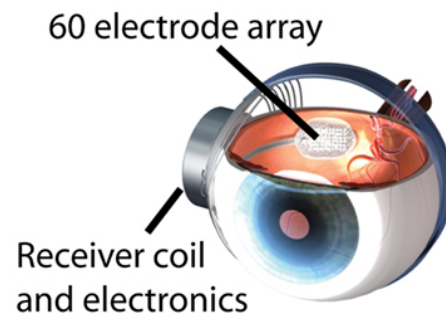
Inspire



Neuropace - RNS System



Second Sight - Argus II



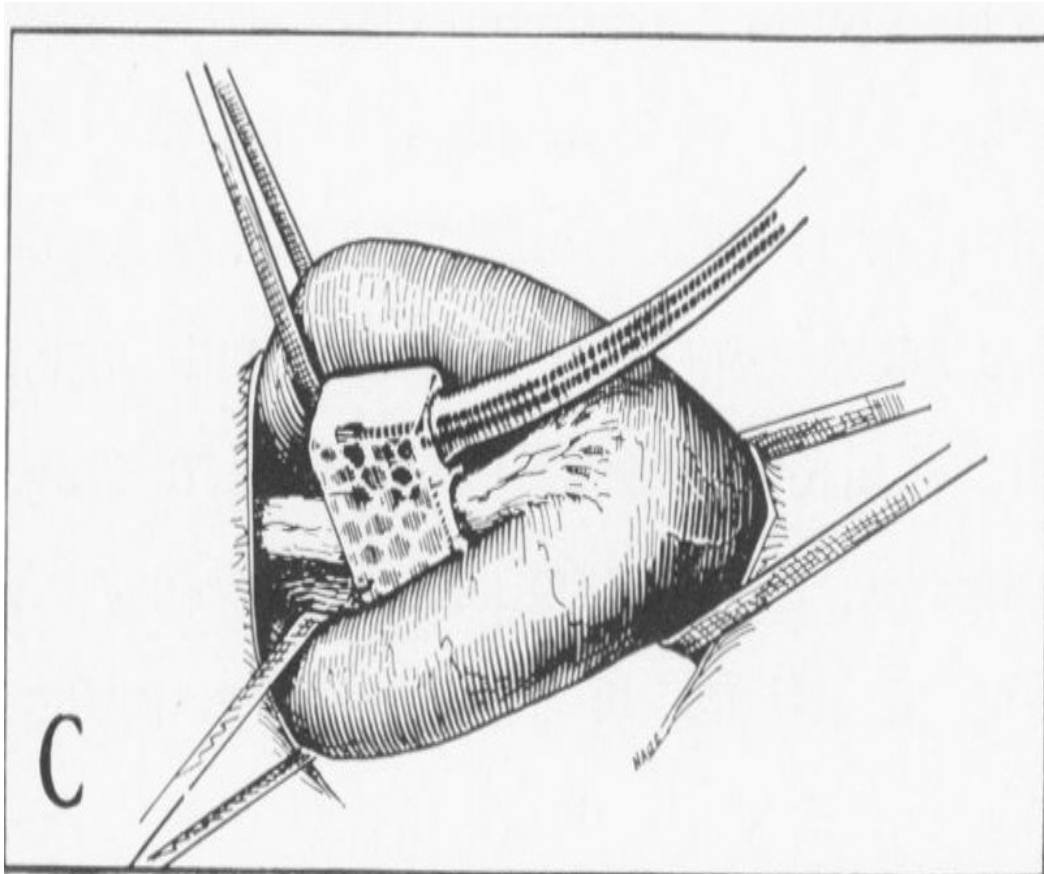
U.S. RCT Pivotal Trials Not Meeting Primary Efficacy Endpoint

- ▶ Medtronic SYMPPLICITY (Renal Denervation)
 - 14 mmHg SAP Drop versus 12 mmHg in Sham Arm
- ▶ CVRx® DEBuT (Baroreceptor Stimulation for Hypertension)
 - Primary: 'On' 54%, 'Off' 46%, >-10 mmHg SAP at 6m
 - Secondary: 42% On, 24% 'Off' <140 SAP at 6m
 - ~50% <140 SAP at 12 months with both arms 'On'
- ▶ Enteromedics EMPOWER
 - 24.4% versus 15.9% in sham Excess Weight Loss at 12 months. Primary endpoint >10 percent difference
 - FDA Panel in June: 8 to 1 safety, 4 to 5 efficacy; 6 to 2 for approval (1 abstention)
- ▶ BROADEN/RECLAIM Trials for Depression

Video: CVRx® Neo



Comparison: Clinical Nerve Cuffs Past and Present



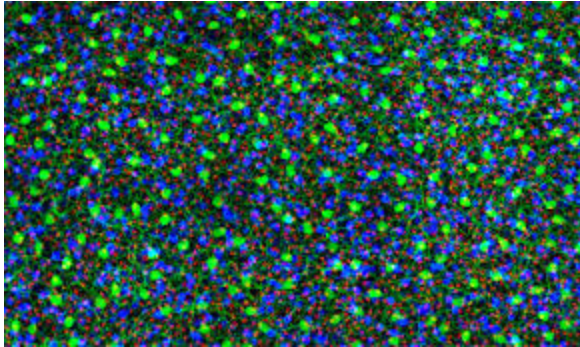
Braunwald 1970



Cyberonics via Getty Images

Why No Higher Resolution Device?

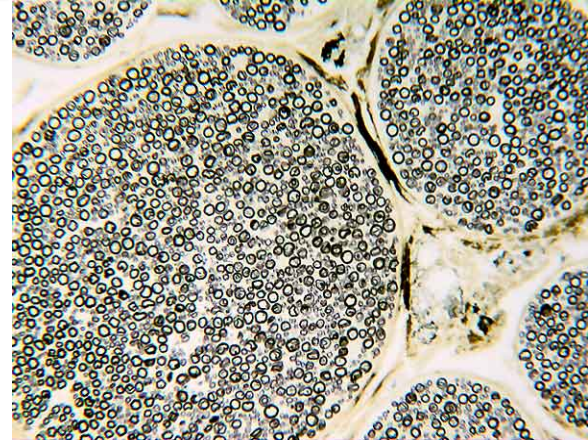
Retina vs. Vagus



Regular, identifiable retinal mosaic

<http://webvision.med.utah.edu/2012/02/retinal-half-mosaic/>

Retina/Cochlea: Consistent functional maps



~100,000 Fibers in Vagus Nerve

<http://vanat.cvm.umn.edu/neurLab1/nerves.html>

PNS: No technology to create high-resolution functional maps (until now)

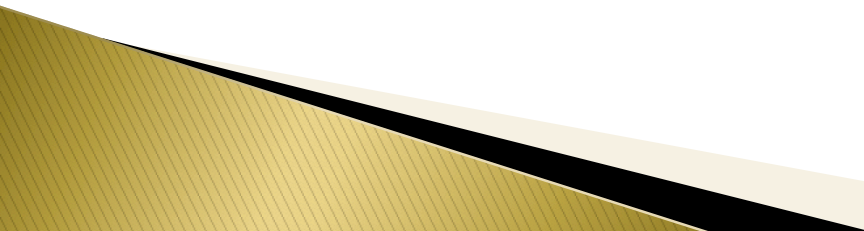
- Manufacturing complexity
- Regulatory burden
- Start-ups: No revenue
- Benefits/Risks/Costs

Bioelectronic Medicines Summit – Dec 16–17, 2013

~140 Attendees, from a range of disciplines across a dozen organ systems and technologies

“electrophysiologists, nanotechnologists, neural engineers, bioinformaticians, disease biologists, material scientists, surgeons, and several neuromodulation companies”

Objectives

- Explore state-of-the-art in sciences underpinning neuromodulation of organ systems
 - Identify / prioritize key research challenges
 - Arrive at \$1M innovation prize challenge
- 

Summit Recommendations/Roadmap

Nature Reviews: Drug Discovery

Topic #1: Creation of a Visceral Nerve Atlas

Objective 1: 'Structural Mapping'

Objective 2: 'Functional Mapping'

Topic #2: Advancement of Interface Technology

Objective 1: 'Electrodes for Visceral Nerves'

Objective 2: 'Signal Imaging and Actuation'

Objective 3: 'Sensing of Organ Functions'

Objective 4: 'Visceral Control Modules'

Topic #3: Early Establishment of Therapeutic Feasibility

Objective 1: 'Proof of Principle'

Objective 2: 'Treatment Codes'

Objective 3: 'Long-term Responses'

Summary: NIH and Non-NIH Portfolio Analyses

Current NIH Investments in Neuromodulation Therapy Development ~\$100M per Year

- Leading Contributors NINDS, NIDCD, NEI, NIBIB, NHLBI and NICHD
- ~\$10M in Device Therapies to Control Visceral Organ Systems

Current NIH Investments in Neural Innervation of Visceral Organ Systems ~\$120M per Year

- Leading Contributors NHLBI, NIDDK and NINDS
- Largest Investments in Cardiorenal/Gastrointestinal Systems
- Anatomical/Functional Mapping a Smaller Subset

Current NIH Investments in Translating Next-Generation Technology to Visceral Nerves ~\$10M per Year

~\$25M in Non-NIH/DARPA Funding
for Neuromodulation, Almost None for
Organ Control

DARPA/Industry/FDA – Demonstrations/Proof of Principle

DARPA Efforts

- HAPTIX Program – Sensory Prosthetics
- Possible Programs in Inflammation, Adrenal Control

GSK Efforts (~\$50M)

- Quick fail in animal models for Diabetes, IBD, RA, Hypertension, Asthma/COPD, OAB, Infertility, Adrenal Control
- \$1M catalytic challenge
- Seed-funding for next-generation technology

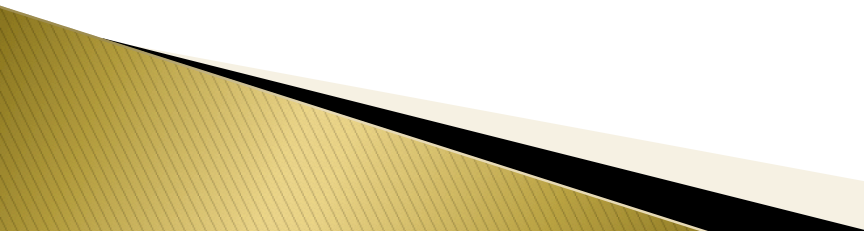
Other Industry Efforts

- Ongoing efforts in numerous large-market indications
- Small markets not well addressed
- FDA/Industry Feedback: ‘Common clinical platform’ for high-resolution stim/record not viable

S.P.A.R.C. Program Objective

This Program will capitalize on recent advances in technology – and anticipated new technology developments facilitated by the Program – to deliver detailed, integrated functional and anatomical neural circuit maps in organ systems

These maps will be directly leveraged to develop and pilot novel electrode designs, with corresponding stimulation protocols and minimally invasive surgical procedures, to improve existing neuromodulation therapies or pursue new indications.



Key Context


Expertise Required – Biology (Not Exhaustive)

- Function of each organ
- Anatomical innervation of each organ and neurobiology
- Surgeons who routinely access nerves for each organ
- Computational modeling of neural activity and organ function
- Post-mortem tracing in humans

Expertise Required-Technology (Not Exhaustive)

- Electrode design - fabrication
- Implantable optogenetic platforms
- Voltage probes/microscopy
- Non-invasive imaging
- Translational engineers
- Clinical devices for functional mapping

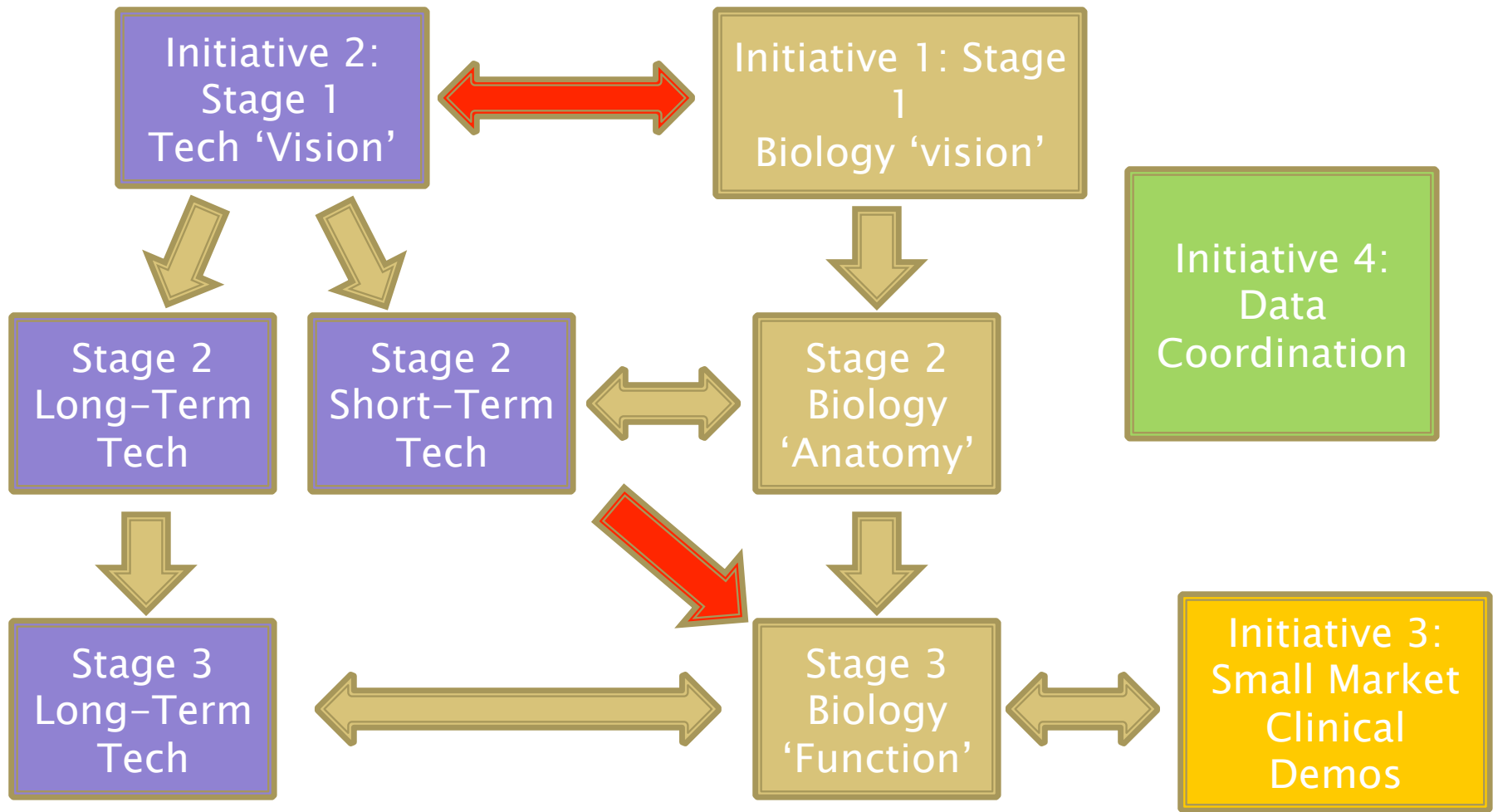
NIH and extra-NIH portfolio analyses indicate these areas of expertise are traditionally siloed, and typically have not coalesced into cohesive teams on their own!



Flexible Structure with Active Management

- Current state of knowledge and technology readiness for each organ system varies widely
- Technologies needed to enable biological goals will develop along different timelines
- Highly responsive and fluid Program through use of Other Transactions Authority and aggressive, adaptive Project Management
- Staged Initiatives, short Stage 1 with “vision setting” grants:
 - The PM will actively facilitate the interactions between teams to create cohesive proposals for Stage 2
 - Budgets, timelines, and milestones for now are ‘reasonable estimates’; milestones will be developed with PM on a project by project basis during Stage 1 and beyond
- Flexibility to optimize opportunities based on proposals and progress

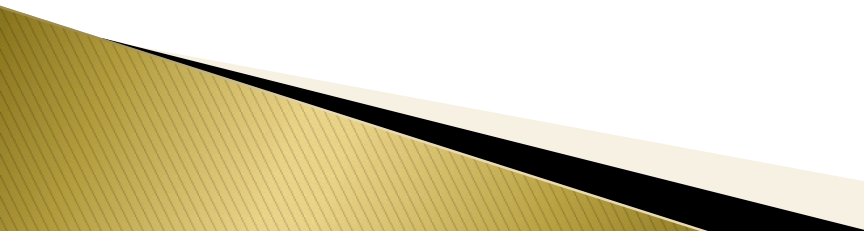
Program Outline: 4 Initiatives, 3 Stages



Initiative #1: 'Biology'

Stage 1: "Vision Setting" Grants

Key Deliverables:

- Assessment of current knowledge one or more organs/systems
 - Identification of opportunities for anatomic and functional mapping in human clinical and post-mortem studies for each organ system (Industry Collaboration, Scientific Payload)
 - Plan to assess inter-individual variability at logical points for surgical intervention
 - A proposal for Stage 2 Biology, using existing technologies for anatomical mapping (details in coming slides)
 - Plan to incorporate emerging technologies from Initiative 2 (Next-Generation Tools) throughout Stage 2 and Stage 3 of the Biology Initiative for functional mapping
- 

Initiative #1: 'Biology'

Stage 2: Mapping Utilizing Existing Technology (Years 1-3)

Key Deliverables:

- Anatomical assessment of cell-types and their variability at potential points for therapeutic intervention
- Post-mortem human assessment
- Low-resolution electrode recordings at interventional points
 - Assess recordings as a biomarker for organ function/therapy outcomes
- Initial functional mapping using low resolution stimulation electrodes (acute, chronic)
- Development and validation of organ specific technology to measure organ function
- Integration of reverse translational projects (Industry Collaboration)

Initiative #1: 'Biology'

Stage 3: Functional Mapping with Next-Generation Tools, Design and Piloting of New Therapies (Years 2-6.5)

Key Deliverables:

Years 2-4: Technologies from Initiative 2 incorporated

- Higher resolution functional mapping with cell-type specificity

Years 4-6.5: Develop and pilot novel neuromodulation strategies

- Based on functional new functional maps

Years 5-6.5: Iterative refinement of long-term technology in biological test-beds (details next slide)

Initiative #2: 'Next Generation Tools/Technology'

Stage 1: Vision Setting Grants

Key Deliverables:

A proposal for Stage 2, for one or more technologies, including:

- Assessment of needs for Biology Stages 2 & 3 (next slides)
- Metric-driven design criteria for validation
- Development of quarterly milestones for short-term deliverables, including plans for iterative refinement with the Biology teams
- A plan for scalable and sustainable manufacture for dissemination to the broader community for Stage 2 and Stage 3 tech

Initiative #2: 'Next Generation Tools'

Stage 2: Short-Term Development (Years 1-3)

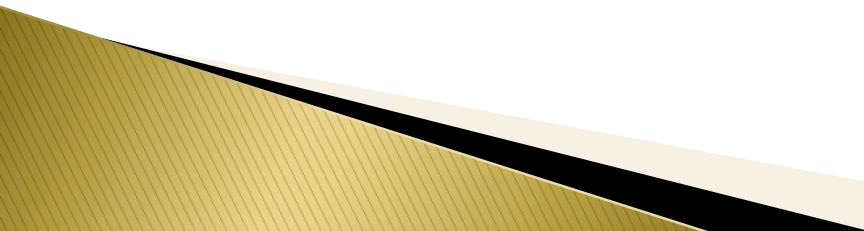
Key Deliverables:

- Robust, wireless low resolution recordings/stimulation for manipulation of the system (2 years)
- Technology platform for optogenetic light sources tailored for the PNS
 - Cell-type specific optogenetic transfection
- Techniques in PNS to identify nerves that have been stimulated and assess local changes in neural structure or function
- Technology and techniques for cell-type specific anatomical mapping in humans post-mortem

Initiative #2: 'Next Generation Tools'

Stage 3: Long-Term Development (Years 1–6.5)

Key Deliverables:

- Wireless, high-resolution system scalable to multiple nerves
 - Techniques for cell-type specific manipulation in larger animal models
 - Sensing probes and associated technologies (Ex: Weiland)
 - Safe non-invasive transcutaneous stimulation techniques (ultrasound, magnetic)
 - Microendoscopic tools to facilitate minimally invasive surgeries for placement of these devices in humans
 - Non-Invasive functional imaging tools optimized for use in the PNS
- 

Initiative #3: 'Clinical Demonstrations for Small Market Indications'

Motivation:

- Modeled after NCATS Discovering New Uses for Existing Molecules
- Therapy targets for small markets will require additional NIH commitment
- Quick demonstration of proof-of-concept in humans using existing devices -> Prioritize for Biology Initiative

Expectation:

- May be very few initially
- Reserved funds for 'up to 3' clinical projects (may award 0 in a year)

FDA and Industry enthusiastic about collaborating

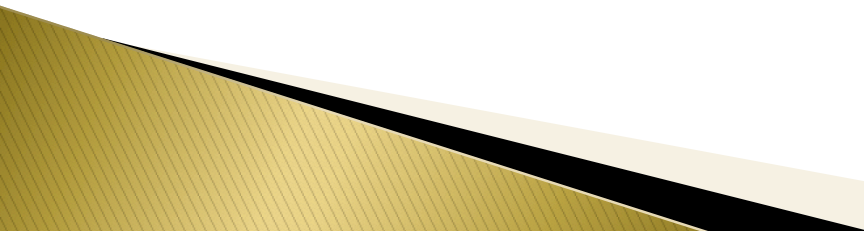
Initiative #4: 'Data Coordination' (Years 2–6)

Objectives:

Develop community resource for data from all biology and technology projects:

- Anatomical mapping and functional mapping by cell-type
- User-friendly data analysis computational tools
- Incorporate next generation computational models of stimulation to facilitate new therapy designs

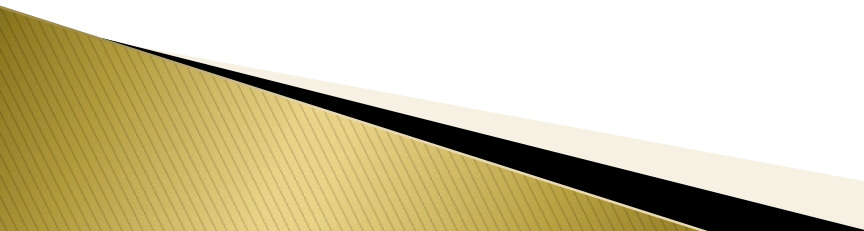
Expectation:

- Data fields and needs for this resource are currently undefined
 - Project Teams will help define initial needs and goals for the Data Coordination Initiative
- 

Breakdown of SPARC Budget – 248 million dollars over 6.5 years

	FY15	FY16	FY17	FY18	FY19	FY20	FY21
Initiative 1 – Biology							
Stage 1	3.5						
Stage 2		20	20	20			
Stage 3					25	25	25
Initiative 2 – Next Generation Technology							
Stage 1	2.5						
Stage 2		5	5	5			
Stage 3		8	8	8	8	8	8
Initiative 3 – Small Market Indications		5.25	5.25	5.25	5.25	5.25	5.25
Initiative 4 – Data Coordination Center		1.25	2.25	2.25	2.25	2.25	2.25
Total	6	39.5	40.5	40.5	40.5	40.5	40.5

Plans for FY15

- ▶ Issue Request for Information from Interested Academic and Industry Partners
 - ▶ Outreach for S.P.A.R.C. Program
 - ▶ Recruit Program Manager
 - ▶ Issue Announcement(s) for Applications
 - ▶ Make Awards for Stage 1 Research Projects
- 

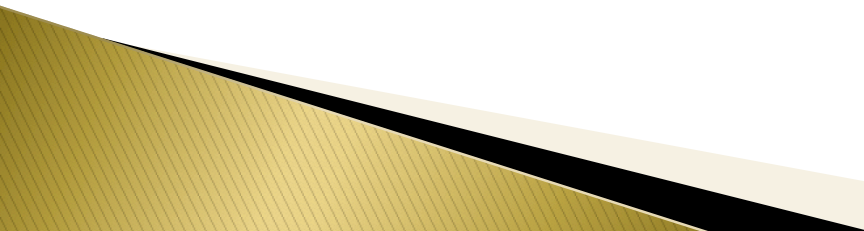
Acknowledgments:

The S.P.A.R.C. Common Fund Team

- ▶ Co-Chairs: Story Landis, Chris Austin, Roderick Pettigrew
- ▶ Team Leads:
 - Greg Germino, NIDDK (Biology)
 - Grace Peng, NIBIB (Next Generation)
 - Dan Tagle, NCATS (Proof of Principle/Demonstrations)
- ▶ Team Members
 - Ned Talley (NINDS), Jim Gnadl (NINDS), Daofen Chen (NINDS), Bill Heetderks (NIBIB), Paul Kimmel (NIDDK), Albert Lee (NHLBI), Mike Weinrich (NICHD), Roger Miller (NIDCD), Ralph Nitkin (NICHD), Theresa Cruz (NICHD), James Coulombe (NICHD), Tom Esch (NIAID), Roger Sorenson (NIDA), Matt McMahon (NEI), Andrew Rossi (NIMH)
- ▶ OD
 - Jim Anderson, Betsy Wilder, Mary Perry, Rob Harriman, Christine Mueller, Scott Jackson
- ▶ Special Thanks
 - Liz Webber (NINDS), Miriam Leenders (NINDS), Debbi Bergstrom (NINDS), Lyn Jakeman (NINDS)

Back-Up Slides

Program Management Structure

- Program Manager (PM) and associated staff will work within the Office of Strategic Coordination, and report to DPCPSI Director
 - OTA awards will be issued through NCATS
 - PM with advice from S.P.A.R.C. advisory committee (CFWG), and final approval by DPCPSI Director
 - For OTA awards, at any point the PM can bring in new expertise by input, and issuing new awards or supplementing existing awards
 - Non-OTA awards will be issued and administered by most appropriate Institute
 - Frequent interactions with investigators, including monthly phone calls, site visits with outside experts, and yearly workshops across projects
 - Reference: DARPA HAPTIX ~\$54M over 4 years has a dedicated staff of 4
- 

Summit Agenda

Seven pre-meeting webinars

- Four focused on nerve interface techniques and hurdles
- Three focused on neurobiology associated with end-organ physiology and disease

Nine breakout groups, each charged with formulating a fundamental challenge and creating a roadmap

Three themes:

- i. Technologies for peripheral nerve interfacing and biomarker recording
- ii. Neurobiology of peripheral organ and system physiology
- iii. Therapeutic possibilities and hurdles